

Chapter 2

Advances in Research on the Mechanisms of Selenium–Mercury Interactions and Health Risk Assessment

A large number of scientific studies have confirmed that interactions between selenium (Se) and mercury (Hg) are a very important topic of study for the systematic understanding of the environmental behavior, fate and toxicological effects of Hg (or Se). In addition, related research involves geology, medicine and many sectors in other disciplines. Research results concerning the interaction characteristics, rules and mechanisms of these two elements in many media, such as water, soils and organisms, are spread out over many segments of the literature. Even with an extensive knowledge base, it is still a challenging task to reveal and organize a clear context and to evaluate environmental and health-related effects and risks. Fortunately, some outstanding researchers have devoted valuable time to writing many comprehensive review articles in their fields (e.g., Skerfving (1978); Berlin (1978); Pelletier (1986); Cuvinaralar and Furness (1991); Falnoga and Tusek-Znidaric (2007); Gailer (2007); Yang et al. (2008) and Khan et al. (2009)), which provided the author with the opportunity to review these excellent articles and other literature. Based on these readings, the author has further organized and integrated many diverse yet related studies and understandings into a relatively complete knowledge system. The aim was to build a bridge between basic research and the application of specific knowledge, with the addition of further personal considerations and ideas. However, it should be noted that although the author has set a very ambitious goal and exerted efforts toward achieving that goal, some of the discussions presented below may inevitably be biased or insufficiently thorough because of the author's limited capability and knowledge. Nevertheless, through comparative analysis and discussion of the following information, it was possible to investigate and elucidate some behavioral characteristics and patterns of Se–Hg interactions that were previously unknown or, at least, did not attract much attention from researchers. This study includes Se–Hg interactions in aquatic ecosystems and terrestrial ecosystems, the physiological significance and metabolic processes of Se and an understanding of the toxicity of Hg exposure. These findings are of great significance for us in the dialectical and objective consideration of the interactions between and effects of Se and Hg and in the comprehensive evaluation of the environmental and health risks of these two elements.

2.1 Selenium–Mercury Interactions and Their Mechanisms in Aquatic Ecosystems

It is well known that the methylation process that converts inorganic Hg (Hg^{2+}) into MeHg (CH_3Hg^+) occurs primarily in aquatic ecosystems and wetlands systems (Ullrich et al. 2001). Because CH_3Hg^+ is one form of Hg that is of the most concern for aquatic ecosystems, resolving the question of how to effectively control the methylation of Hg in sediment and water has become an urgent task for the scientific community (Yang et al. 2008). However, compared with studies of mammals and humans, to date, studies of Se–Hg interactions in aquatic ecosystems have remained relatively scarce. The major discovery in recent years that Se can inhibit the toxicity and enrichment of MeHg in aquatic organisms has provided a potential approach to solving the problem of Hg contamination in water (Yang et al. 2008). Research indicates that adding Se to lake sediments can significantly reduce the formation of MeHg in these sediments. Jin et al. have added Na_2SeO_3 in various concentrations (0–12.5 $\mu\text{g/g}$ of wet weight) and HgCl_2 at a fixed concentration (50 $\mu\text{g/g}$) to lake sediments and placed these sediments in an anaerobic environment for 25–70 days at 20–37°C (Jin et al. 1997, 1999). The results demonstrate that Se can also significantly reduce the generation of MeHg, even at low concentrations (0.25 $\mu\text{g/g}$), and the more Se is added, the less MeHg is generated. Cheng et al. and Belzile et al. have also found, in field studies, that the total Hg and MeHg concentrations in lakes and in the organisms of the lakes were inversely correlated with the dissolved Se in the lake water and the total Se in the organisms (Belzile et al. 2006a; Chen et al. 2001). Many early studies of aquatic ecosystems have also shown that Se might inhibit the enrichment of Hg in the food chain (Jin et al. 1999; Paulsson and Lundbergh 1989; Southworth et al. 2000). Yang et al. have summarized three possible mechanisms for these phenomena as follows (Yang et al. 2008):

- (i) Non-biological processes (with no bacterial reduction involved) directly generate an insoluble inert gel compound, HgSe , which causes sedimentation and thereby inhibits Hg methylation; the formulae for the reaction are as follows: $\text{Hg}^{2+} + \text{Se}^{2-} = \text{HgSe}$ and $\text{Hg}^0 + \text{Se}^0 = \text{HgSe}$.

The dissolution and precipitation constant of HgSe (10^{-58} to 10^{-65}) is much smaller than that of HgS (10^{-52}) (Björnberg et al. 1988; Dyrssen and Wedborg 1991); therefore, it is very likely for Hg^{2+} to first react with Se^{2-} to form the HgSe compound and then precipitate (Yang et al. 2008). The reaction between Hg^0 and HSe^- is similar to the above reaction, resulting in halted or greatly reduced Hg methylation in aquatic ecosystems (Yang et al. 2008). In aquatic ecosystems, Se^{2-} (HSe^-) and Se^0 can be generated through the microorganism-related metabolism of organic Se or inorganic Se compounds (Hockin and Gadd 2003). Se^0 may also be formed without involving microorganisms, for example, through the reaction between selenite and Fe^{2+} or dissolved S^{2-} under anaerobic conditions

(Yang et al. 2008). Because $\text{Se}^{2-}(\text{HSe}^-)$ is more acidic than H_2S (McNeal and Balistrieri 1989), $\text{Se}^{2-}(\text{HSe}^-)$ should react with Hg^{2+} to form the HgSe compound more easily than does HSe^- , and the product (the HgSe compound) is more insoluble than HgS (Yang et al. 2008). After comparing the formation constant and bond strength of CH_3Hg^+ , SeCN and $\text{CH}_3\text{Hg}-\text{SCN}$, Carty and Malone have expressed the belief that the interaction between Hg and Se is stronger than the interaction between Hg and S (Carty and Malone 1979).

- (ii) Formation of the $(\text{CH}_3\text{Hg})_2\text{Se}$ complex to facilitate the demethylation of CH_3Hg^+ ; the reaction is as follows: $\text{HSe}^- + 2\text{CH}_3\text{Hg}^+ = \text{CH}_3\text{Hg}-\text{Se}-\text{HgCH}_3 = \text{CH}_3-\text{Hg}-\text{CH}_3 + \text{HgSe}$.

Photolysis is an important abiotic process for the demethylation of MeHg in the environment (Ullrich et al. 2001), and the presence of sulfide can promote this process (Yang et al. 2008). Baughman et al. have found that CH_3Hg^+ , in the forms of CH_3HgS^- , $(\text{CH}_3\text{Hg})_2\text{S}$ and $\text{CH}_3\text{Hg}-\text{SH}$, can be rapidly decomposed into HgS under UV irradiation and then precipitate. This decomposition is more rapid than that of CH_3HgCl or CH_3HgOH , which may be attributed to the fact that the UV absorption capacity is weak in the latter two forms (Baughman et al. 1973). However, these authors have also found that $(\text{CH}_3\text{Hg})_2\text{S}$ decomposition can occur in the dark to form HgS . The relevant reaction may be the following: $\text{HS}^- + 2\text{CH}_3\text{Hg}^+ = \text{CH}_3\text{Hg}-\text{S}-\text{HgCH}_3 = \text{CH}_3-\text{Hg}-\text{CH}_3 + \text{HgS}$ (Craig and Moreton 1984). Because Se and S have similar properties and Se can bind Hg more strongly than does S, it is speculated that Se may play a similar role to that of S in the demethylation of MeHg (Yang et al. 2008). Selenides formed in aquatic ecosystems may react with CH_3Hg^+ to form an unstable complex $(\text{CH}_3\text{Hg})_2\text{Se}$, and eventually decompose into insoluble stable HgSe (Yang et al. 2008). Se^{2-} can bind to CH_3Hg^+ more tightly than does S^{2-} ; thus, the $\text{Se}^{2-}(\text{HSe}^-)$ in sediments is more capable than $\text{S}^{2-}(\text{HS}^-)$ of taking CH_3Hg^+ away from other ligands (Carty and Malone 1979).

- (iii) Higher absorption of Se by organisms leads to stronger “repulsion” against MeHg absorption.

Although the results of laboratory studies of certain animal tissues indicate that the simultaneous application of Hg^{2+} and SeO_3^{2-} can increase Hg absorption, the field and laboratory studies of bacteria (*Pseudomonas fluorescens*) conducted by both Belzile et al. and Chen et al. have clearly demonstrated that Se and Hg are inversely correlated (Belzile et al. 2006a; Chen et al. 2001); namely, the higher is the Se content in the blood plasma of aquatic organisms or unicellular bacteria, the lower are the levels of total Hg and MeHg . A similar phenomenon has also been observed in the muscles, livers and brains of fish (Yang et al. 2008). In addition, studies conducted by Chen et al. and Belzile et al. have shown that increasing the Se intake of organisms from water and food (in excess of normal nutritional needs but still below toxic levels) will increase the turnover rate of Se in the organisms (absorption and excretion) (Belzile et al. 2006a; Chen et al. 2001). The metabolites of the Se, such as $\text{Se}^{2-}(\text{HSe}^-)$, CH_3Se^- and selenocysteine (SeCys), will readily

bind the CH_3Hg^+ that is absorbed by the organism because of the strong affinity of these metabolites for CH_3Hg^+ , thus inhibiting or reducing the binding of CH_3Hg^+ to cells in the organism and inhibiting the toxicity of CH_3Hg^+ to the organism (Yang et al. 2008). Under the assumption that the absorption rate of CH_3Hg^+ from foods is the same in both an Se-rich and an Se-poor environment, organisms in the Se-rich environment will be better able to remove CH_3Hg^+ . Studies conducted by Belzile et al. have indeed indicated lower CH_3Hg^+ concentrations in organisms with higher Se contents (Belzile et al. 2006a).

2.2 Selenium–Mercury Interactions and Their Mechanisms in Terrestrial Ecosystems

There have been many studies of the inhibitive effects of Se on Hg^{2+} and CH_3Hg^+ in aquatic ecosystems. In contrast, there has been an almost total lack of similar studies for terrestrial ecosystems. If Se can fix the Hg in terrestrial ecosystems (such as soils) in stable forms (such as HgSe), then the surface runoff should carry much less Hg from mountain soils to downstream river and lake systems, thus reducing the Hg methylation that may occur in these aquatic ecosystems (Yang et al. 2008). Early experiments performed by Shanker et al. seem to confirm this hypothesis (Shanker et al. 1996a, b). These authors have confirmed through their experiments that if selenites (or selenates) were added to soils containing HgCl_2 solution, then the Hg enrichment in plants (tomato and radish) grown in these soils would be reduced. A possible explanation for this finding is that Se and Hg react and form the insoluble compound HgSe , which then precipitates, thereby inhibiting the absorption of Hg in plants (Yang et al. 2008).

A few recent studies of Se-rich plants (including soybeans (Yathavakilla and Caruso 2007), mustard (Mounicou et al. 2006a, b) and onions (Afton and Caruso 2009; Zhao et al. 2013a, b) have been conducted, primarily under controlled conditions using laboratory simulation, and have focused on the mutual constraints placed by Se and inorganic Hg on each other. However, the results of these few studies of Se-rich plants clearly demonstrate that increasing the supply of Se in rhizosphere soils can significantly inhibit the accumulation of inorganic Hg in the portions of plants above the roots. These studies suggest that increasing the Se in rhizosphere soils may inhibit the absorption, transportation and enrichment of rhizosphere inorganic Hg in the portions of plants above the roots. This result may be related to the formation of HgSe compounds (chelates of Hg and Se, molar ratio 1:1) in the rhizosphere environment or the root tissues. McNear et al. have used X-ray absorption near-edge structure (XANES) and synchrotron-radiation X-ray fluorescence spectroscopy (SXRF) techniques to confirm the presence of an inert substance, HgSe , on the surfaces of roots (McNear et al. 2012).

As early as 1975, Bao et al. discovered the existence of an extremely rare independent mineral of HgSe in the Hg mine in Wanshan (Bao 1975). It is well

known that Se and S are very similar in crystal chemistry and in some of their geochemical properties. For example, they have the same atomic structure, the same charge (S^{2-} , Se^{2-}) and similar atomic radii (S: 0.104 nm, Se: 0.161 nm) and ionic radii (S: 0.184 nm, Se: 0.191 nm), and therefore, Se can easily be incorporated into the crystalline lattices of sulfides. Se is a trace element in HgS, where Se can replace S to form the HgS–HgSe isomorphous series. In an Hg- and Se-rich hydrothermal solution that lacks S or has S in the form of sulfate ions, i.e., SO_4^{2-} ions participate in the mineralization at a high potential, Se can easily replace S to form the extremely rare independent mineral HgSe (Bao 1975; Bao and Bao 1995).

For plants, the formation of HgSe precipitates in the rhizosphere environment will significantly reduce the Hg and Se absorption and transport in the plants, whereas for the entire food web of an aquatic ecosystem, the fixation by Se and the formation of HgSe at each level of the food chain can reduce the absorption and enrichment of MeHg in organisms in the upper tier of the food chain. This mechanism may explain why the levels of Se in lake water can affect the MeHg enrichment in food chains. This speculation has been confirmed by related studies (Belzile et al. 2009; Peterson et al. 2009a, b). This process is continuously involved in the biogeochemical cycling of Hg and the “seizing” or “solidification” of available Hg, resulting in low Hg levels in fish in some Se-rich areas. In contrast, the absence of available Se will lead to an increase in the Hg levels in fish. This understanding provides a certain motivation for using the “repulsion” between Se and Hg to assist plants or aquatic organisms in inhibiting the absorption and accumulation of MeHg by adding Se to soils or lakes. However, the specific effects and mechanisms of the use of Se to inhibit Hg absorption and accumulation still require further study.

It is worth emphasizing that many people are familiar with “the protective effect of Se against the toxicity of Hg,” but in contrast, few people recognize the importance of the fact that “Hg also inhibits Se toxicity” (Klimstra et al. 2012). If an excessive amount of Se were added to the environment, not only would the expected inhibition of Hg absorption and enrichment not be achieved but aquatic organisms or plants might also suffer from Se toxicity. This situation, in turn, would activate the physiological mechanisms of the affected organisms to increase their absorption and accumulation of Hg to resist the toxicity of Se, eventually leading to environmental and health-related risks caused by Hg and Se contamination. This phenomenon has been observed in early studies using mammals: adding Se in amounts beyond the reasonable range for safety caused an “additive effect” or “synergistic effect” of HgSe toxicity instead of the desired “antagonistic effect” (Yang et al. 2008). Southworth has proposed that the total dissolved Se concentration in water should not exceed the safe range of 5 $\mu\text{g/L}$ when Se is added to reduce the MeHg enrichment in fish (Southworth et al. 2000). Paulsson and Lundbergh have found that the Hg level in fish muscle tissues was indeed significantly reduced when the concentration of total dissolved Se was changed from 0.4 to 3–5 $\mu\text{g/L}$ (Paulsson and Lundbergh 1989). In addition to the necessity for careful consideration of the amount of Se to be added to an environment, there are many environmental factors involved in controlling the chelation between Se and Hg in

soils and the period required to achieve the “solidification” of Se and Hg chelation; these environmental factors should also be taken into account, and the long-term effects of Se addition in various circumstances still require thorough study.

2.3 Mechanisms of Selenium–Mercury Interactions in Mammals (and Humans)

The inhibitive effects of Se on the toxicity of inorganic Hg and MeHg in animals were first reported long ago. One of the earliest reports was from an experiment conducted by Parizek et al., in which they found that Se could inhibit Hg^{2+} toxicity in animals (Pařízek and Ošťádalová 1967). A few years later in 1972, Ganther et al. discovered that Se had similar effects on MeHg toxicity in animals (Ganther et al. 1972), and the antagonistic effect of Se on inorganic mercury and MeHg was confirmed by a series of later tests (Belzile et al. 2006a, b; Beyrouthy and Chan 2006; Chen et al. 2001; Newland et al. 2006). In addition, the Hg-to-Se molar ratio was found to be 1:1 in experiments on marine mammals (Koeman et al. 1973, 1975) and mercury-mine workers (kidney, liver and muscle tissues) (Kosta et al. 1975) as well as the urine of mercury miners and local residents in Hg mine areas (Chen et al. 2006). Animal studies have indicated that the toxic effects of MeHg increase with decreasing Se intake. For critical tissues such as those of the brain, the toxic effect is directly correlated to the Hg-to-Se molar ratio and is dramatically enhanced when this ratio is greater than 1:1 (Brockman et al. 2011). In a recent study, rats exhibited severe symptoms of MeHg poisoning when fed with foods of high MeHg/Se molar concentration. In contrast, when fed with foods that contained the same MeHg dose but an increased Se content, i.e., a decreased MeHg/Se molar ratio, the rats did not exhibit symptoms of MeHg poisoning (Ralston et al. 2008). A large number of animal studies have shown that increasing dietary Se intake within a physiologically appropriate range can significantly increase the detoxification signal for symptoms of MeHg poisoning (Beyrouthy and Chan 2006; Møller-Madsen and Danscher 1991; Ralston et al. 2007, 2008). Recently, Li et al. have conducted a case study focused on residents in Hg mine areas with inorganic Hg poisoning, and the results indicate that moderate supplementation with organic Se can increase the Hg excretion in local residents (Li et al. 2012).

2.3.1 Protective Effects of Selenium Against Mercury Toxicity and the Mechanisms Thereof

Although Mergler et al. believe that there is no very clear evidence that Se can inhibit the toxicity of MeHg (Mergler et al. 2007), Yang et al. (2008) have stated, after conducting extensive analysis and research, the results of many studies still

tend to support the inhibitory effect of Se on Hg and MeHg. On the basis of previous reports, Khan and Wang have further categorized the related mechanisms into the following six types (Khan and Wang 2009):

(i) The formation of the MeHg-Se complex

The MeHg-SR complex is considered to be the predominant form of MeHg in cellular environments (-SR is a sulfur-containing amino acid) (Khan and Wang 2009; Lemes and Wang 2009) because of the presence of a large number of -SH groups in biological molecules and their affinity for MeHg⁺ (Reid and Rabenstein 1981). Although MeHg and -SH have very high formation constants (10^{15} to 10^{17}) (Reid and Rabenstein 1981), the MeHg-SR complex is unusually stable and can withstand the rapid ligand exchange reaction in aqueous solution (Rabenstein et al. 1982). A similar situation may even occur in biological systems (Rabenstein 1978). Researchers have proposed several hypothetical chemical mechanisms (such as associative, dissociative, bridging) to explain these rapid ligand exchange reactions, but the replacement of thiol compounds with free -SH via complexation appears to play a major role (Rabenstein and Reid 1984). Because the binding is stronger in MeHg-SeR than in MeHgSR (Arnold et al. 1982), and the formation constant of -SeH complexes is greater than that of MeHg-SH, a complex of -SH, the ligand exchange between -SR and -SeR can occur rapidly, thereby promoting the formation of the MeHg-Se complex (Arnold et al. 1986). The biological availability of the MeHg-SeR complex is lower than that of MeHg-SR because of the stronger binding affinity of Hg–Se (Arnold et al. 1982). Therefore, the formation of the MeHg-SeR complex can reduce the toxicity of MeHg but may also induce Se deficiency (Khan and Wang 2009).

(ii) Pro-demethylation effects of selenium

The Hg methylation process is generally considered to be a microbial process that primarily involves sulfate-reducing bacteria (Ekstrom et al. 2003). At present, there is no conclusive evidence that the Hg methylation can occur in vivo in animals or plants (Khan and Wang 2009). However, the opposite process—the demethylation of MeHg—can occur in large quantities in the liver of a mammal once the kidney has gathered inorganic Hg via blood filtration (Magos et al. 1976). Although the mechanism is unknown, Se may be involved in the demethylation of MeHg (Khan and Wang 2009). It has been shown that selenite can increase the cleavage of C–Hg in phenyl Hg in rat livers (Fang 1974). Another possible mechanism for Se to facilitate the demethylation of MeHg is through the formation of dimethyl selenide, which is unstable at physiological temperatures and can be easily decomposed into inorganic HgSe (Khan and Wang 2009). Whether Se is directly involved in the process of MeHg demethylation, the resulting inorganic Hg can be converted into selenide because of the presence of HgSe in the livers and kidneys of marine mammals and sea birds, which has been widely reported (Magos et al. 1976; Rawson et al. 1995). The toxicity of inorganic Hg can be reduced if it can bind selenide to form HgSe or a highly stable HgSe protein complex, which is likely to be a mechanism for mitigating MeHg poisoning in

marine mammals that are high in the food chain and whose MeHg removal rate cannot keep up with their MeHg intake rate (Nigro and Leonzio 1996); this mechanism may explain the 1:1 Hg-to-Se molar ratio in these animals and why high levels of Hg do not appear to induce toxic effects in these animals (Khan and Wang 2009; Lockhart et al. 2005).

(iii) Formation of the Hg–Se complex

Similar to MeHg, Hg–SeR, which is an inorganic form that is less bioavailable, may also reduce the toxicity of inorganic Hg (Khan and Wang 2009). This is because when Se presents in the form of SeO_3^{2-} and Hg presents in the form of HgCl_2 at the same molar concentration, the counteraction between the two is highly effective (Burk et al. 1974b; Chmielnicka et al. 1979; Naganuma et al. 1984; Parizek and Ostadalo 1967). This finding has inspired a group of researchers to propose a $(\text{HgSe})_n$ polymer, which can bind to a particular protein in blood plasma at the same molar ratio (Naganuma et al. 1984). The plasma protein that this complex binds was later identified as selenoproteins P (SeIP) (Yoneda and Suzuki 1997). $(\text{HgSe})_n$ –SeIP is considered to be the precursor of HgSe (Ikemoto et al. 2004). Kosta et al. have found the Hg-to-Se molar ratio to be 1:1 in the brains of people exposed to inorganic Hg, and they believe that this Hg compound has a relatively long biological half-life and that its chemical formula should be related to the structure of the Hg–Se complex (Kosta et al. 1975).

(iv) Redistribution of inorganic Hg inside organisms under the influence of Se

Khan and Wang (2009) have proposed that another possible approach to using Se to mitigate Hg toxicity is to redistribute Hg among various organs in a biological system under the influence of Se. The simultaneous administration of single doses of Se and Hg can increase the concentration of both inside an organism. However, unlike the administration of a single dose of Hg only, there is evidence that administering both Se and Hg at the same time can cause Hg redistribution between the liver and the kidney (Burk et al. 1974a; Chen et al. 1974). Nevertheless, there are also studies that have found no evidence of Se-induced redistribution in animals. Therefore, the existence and reliability of this mechanism remain an open question (Khan and Wang 2009).

(v) Inhibitive effect of Se on freed methyl

The toxicity of MeHg is generally believed to be primarily attributable to the affinity of MeHg^+ or demethylated Hg^{2+} for $-\text{SH}$. However, Ganther has expressed the belief that the toxicity of MeHg may be, at least in part, attributable to the free methyl radicals released from MeHg (Ganther 1978; Khan and Wang 2009). This hypothesis assumes that after MeHg is absorbed by the lipophilic membranes in target tissues (e.g., the brain), MeHg decomposition may occur during the initial phase of aerobic metabolic reactions. Selenium-dependent glutathione peroxidase (GPx) will cause peroxides to decompose, indirectly leading to the decomposition of MeHg (Khan and Wang 2009). This interpretation also applies to the suppression of MeHg toxicity caused by other antioxidants, such as vitamin E.

In addition, it may explain the life cycle of MeHg in the brain because Hg^0 can diffuse into the blood and eventually be transpired out of the body (Khan and Wang 2009). However, there is no direct evidence to support this hypothesis (Khan and Wang 2009).

(vi) Se–Hg complexation-induced Se deficiency

Because the affinity of Hg^{2+} and MeHg^+ for -SeR is higher than for -SR, it is reasonable to assume that Hg and MeHg will bind -SeR with higher priority, resulting in the reduced bioavailability of Se in organisms (Khan and Wang 2009). In fact, for a constant total Se content in biological organs, MeHg has been shown to have inhibitive effects on the activity of GPx (Fredriksson et al. 1993; Nishikido et al. 1987; Watanabe et al. 1999). By assuming the same formation constants for MeHg–GPx complexes and MeHg–SeCys complexes, Arnold et al. estimated that 1.6–47 % of the R–SeH in an organism can complex with MeHg at an MeHg concentration of 1–50 μM (Arnold et al. 1986). Such a decrease in Se bioavailability can be neglected for people with normal plasma MeHg concentrations ($\sim 0.01 \mu\text{M}$) but would require attention for populations exposed to MeHg (Khan and Wang 2009). For example, in the MeHg poisoning case documented in Iraq in 1972, the plasma MeHg concentrations of the victims reached 30 μM (Arnold et al. 1986), which could have reduced the bioavailability of Se by approximately one-third (Khan and Wang 2009). Therefore, the complexation of Se in selenoproteins with HgSe will lead to Se deficiency, causing impairment in the corresponding function of the selenoproteins (Nishikido et al. 1987). The observed toxicity of Hg is at least partially attributable to Se deficiency caused by Se–Hg complexation (Khan and Wang 2009; Watanabe et al. 1999).

Khan and Wang have summarized that, of the six mechanisms described above, the first four are consistent with the conventional assumption that the toxicity of Hg is caused by the Hg^{2+} or MeHg^+ . The latter two are in opposition to the conventional assumption, instead based on the belief that the toxicity of Hg and MeHg (completely or at least for the most part) is indirectly caused by free radicals or the relative deficiency of Se (when the MeHg-to-Se molar ratio $>1:1$) (Khan and Wang 2009). With plenty of evidence continuing to emerge, the last listed mechanism, i.e., the toxicity of MeHg is attributable to the restricted synthesis and activity of selenoenzymes, has recently begun to attract more attention from scientists (Ralston and Raymond 2013; Raymond et al. 2012).

The conventional belief is that maternal exposure to MeHg during pregnancy is directly correlated with later fetal neurodevelopment. Based on this conventional assumption, scientists have performed a series of epidemiological studies in various regions and on various populations to assess the adverse effects of maternal exposure to relatively low doses of MeHg (compared to the high doses of Minamata disease) on fetal development. However, the results of these studies seem to contradict each other (Khan and Wang 2009; Raymond et al. 2012; Raymond and Ralston 2009). Among them, studies of children in New Zealand (Crump et al. 1998) and the Faroe Islands (Grandjean et al. 1997) show evidence of adverse effects on children's health, but studies in the Seychelles Islands (Myers and

Davidson 1998; Myers et al. 2000) did not find any such evidence. Studies from the United Kingdom (Myers et al. 2000), United States (Lederman et al. 2008) and Denmark (Oken et al. 2008), among others, have found that increasing maternal fish consumption (and therefore MeHg exposure) has significant benefits for children's development. Evidently, if we insist on adhering to the conventional concept that “the amount of maternal MeHg exposure is the only factor that determines the outcome of fetal neurodevelopment,” then the differences among the results of these studies cannot be explained.

Inspired by this problem, some researchers have attempted to propose a novel mechanism. In contrast with the conventional mechanism, the assumption of this new mechanism is that “the toxicity of MeHg is not directly correlated with maternal exposure to MeHg but is indirectly (completely or at least for the most part) caused by a relative deficiency in Se (when the MeHg-to-Se molar ratio $>1:1$)” (Khan and Wang 2009). This hypothesis has been recently advocated by Ralston and Raymond et al. They have used this hypothetical mechanism to “successfully” explain the inconsistencies among the epidemiologic surveys from different regions (Ralston 2008; Raymond et al. 2012; Raymond and Ralston 2009).

The statement that “the adverse effect of maternal exposure to MeHg is indirectly correlated with relative deficiency of Se (when the MeHg-to-Se molar ratio $>1:1$)” is based on the recognition that Se has biochemical and physiological functions and metabolic effects. This recognition is very important for understanding the last mechanism (vi: Se-Hg complexation-induced Se deficiency) mentioned above, which is “subversive” to the conventional mechanism. Therefore, it is necessary to devote a portion of this chapter to a brief introduction to this concept.

2.3.2 Implications of the Physiological Significance and Metabolic Processes of Selenium for the Toxicity of Mercury Exposure

As a trace element that is essential for both mammal and humans, Se exists in selenoproteins in two forms, SeCys and selenomethionine (SeMet), and it is involved in the active sites of these selenoproteins, which have important biological functions. Se exerts its biological effects on the antioxidant function, immune function, reproductive function, apoptosis and endocrine hormones of animals through selenoproteins (Kyriakopoulos and Behne 2002; Taylor et al. 2009). As most selenoproteins are important enzymes, selenoproteins are also sometimes called selenoenzymes. Selenoenzymes are critical to biological functions such as controlling the redox reaction in brain and neuroendocrine tissue, especially preventing and reversing oxidative damage (Chen and Berry 2003; Whanger 2001). There are three families of selenoproteins (deiodinase, thioredoxin reductase and

GPx) that play important roles in embryonic development, including cell growth and survival, free-radical detoxification and regulation of the thyroid-hormone metabolism (Kyriakopoulos and Behne 2002). Therefore, the loss of these selenoenzymes and their functions may explain many of the pathological effects of Hg poisoning, including oxidative damage, changes in the glutathione metabolism and the interruption of signal transduction (Raymond et al. 2012).

The main molecular forms of Se in foods are amino acids, SeCys and SeMet (Ralston and Raymond 2010). Prior to the synthesis of selenoproteins, these organic forms of Se must first be degraded into inorganic forms of Se compounds (Ralston 2008). There is an important distinction between SeCys synthesis in animal tissues and SeMet synthesis in plants. In mammals and humans, the physiological and biochemical importance of Se is primarily achieved via the activity of SeCys. SeCys is also sometimes called the 21st amino acid because of its importance as a protein component in mammals.

Studies have shown that MeHg–Cys seems to be the principal form of MeHg present in fish tissues (Harris et al. 2003). This MeHg–Cys adduct is similar to methionine (Met) in its biochemical properties and can cross the placenta and blood-brain barrier as a “molecular imitator” of Met (Bridges and Zalups 2005). Selenides can form within the synthesis cycle of selenocysteine. The binding force between Se and Hg (10^{45}) is nearly one million times that between S and Hg (10^{39}) (Dyrssen and Wedborg 1991; Yang et al. 2008); therefore, Se will bind MeHg with higher priority because of the mass action effect (Raymond et al. 2012). When MeHg–Cys encounters the ionized Se of SeCys in the active sites of selenoenzymes, the S that binds the MeHg in the structure will exchange with the Se in the SeCys, which has a higher binding force, and directly form MeHg–SeCys (Ralston 2008). Exposure to higher doses of MeHg will inevitably lead to an increase in the consumption of SeCys, resulting in the deficiency of available SeCys and affecting normal physiological function. MeHg is therefore considered to be a highly specific, irreversible inhibitor for selenoenzymes (Raymond et al. 2012). This inhibitor not only eliminates the enzyme activity but also limits the release of Se from MeHg–Sec complexes, thus preventing Se from participating in cysteine synthesis and circulation in cells. Ralston and other researchers have recently stressed that damage to selenoenzyme synthesis or the inhibition of selenoenzyme activity may be an important mechanism for MeHg toxicity (Ralston 2008; Ralston and Raymond 2010; Raymond et al. 2012).

2.4 New Model for the Assessment of the Health Risks of Mercury and a Relevant Proposal

At present the Hg concentration is the only standard used in the health-and-safety risk assessment of seafood. It was proposed as early as 1972 that the Hg-to-Se molar ratio should be used as a reference standard for Hg pollution (Ganter et al.

1972). However, this proposal has attracted little attention because the specific underlying mechanism has only gradually become clear in recent years. The results of animal studies conducted by Ralston et al. indicate that using the Hg-to-Se molar ratios of the brain, kidney and liver yields a better prediction of the Hg toxicity than using the MeHg concentration alone (Ralston et al. 2008).

To simplify the evaluation of the risks of MeHg exposure and the nutritional benefits of Se, Kaneko and Ralston have proposed the Se Health Benefit Value (Se-HBV) (Kaneko and Ralston 2007) and have used this index to successfully explain the “contradictory” research results that the conventional Hg-exposure evaluation model fails to explain clearly (Ralston 2008). The Se-HBV combines the absolute values and the relative ratio of Se and Hg, and the relative ratio of the two is used to correct the absolute amounts of Hg and Se. The Se-HBV can measure the risks and benefits of the dietary intake of Hg and Se using only one index, and it is more easily explained than the conventional model in which only Se or Hg is considered. A positive index indicates a health benefit, and a negative index indicates a health risk. The Se-HBV value matches the expected benefits or risks. The two formulas are expressed in molar units to reflect the stoichiometric relation between the two substances. The recommended formula, namely, $\text{Se-HBV} = \text{Se}(\text{Se}/\text{Hg}) - \text{Hg}(\text{Hg}/\text{Se})$, has begun to be used in many recent studies to evaluate and discuss the risks of the combined effects of Se and Hg. Unfortunately, both this formula and the conventional Hg-to-Se molar ratio method have an obvious shortcoming. This shortcoming is as follows: in some extreme cases, in the presence of a lower-than-standard Se intake (i.e., the danger of selenium deficiency) or when the Se intake far exceeds the standard (i.e., the potential for Se poisoning), it is still possible to satisfy the condition of an Hg-to-Se molar ratio >1 , or a positive Se-HBV. These two extreme cases are hidden within this single Se-HBV index and superficially manifest as highly beneficial situations, suggesting that either risk-evaluation method may be somewhat misleading. The author believes that evaluation that places undue emphasis on or uses only the Se-to-Hg molar ratio or the Se-HBV is no better than using only the absolute content of Hg or Se; not one of these approaches is sufficiently cautious.

In addition, the specific Hg-to-Se molar-ratio threshold for the production of protective effects is presently unknown. Logically speaking, it is also very difficult to determine a universal ratio because of the differences in such aspects as physiology and dietary habits among various regions and populations. More importantly, recent studies have found that there is no apparent threshold for the toxic effects of MeHg exposure (Groth 2010). Therefore, based on the considerations of controllability and “conservative principles” in risk management (i.e., one would rather underestimate the health benefits and overestimate the risks in uncertain conditions), the author suggests that it is best to combine the conventional intake-dose-only index and the newly proposed index of the Se-to-Hg molar ratio, which permits the comparison of various combined relations. The purpose is not to define an “accurate” measure of the relative risks and benefits but instead to use this comparative assessment model as a guide for the general population and government consultation. This proposal is aimed at garnering the greatest health

benefits and simultaneously minimizing the risks in the formulation or implementation of management strategies. For example, when both the Hg-to-Se molar ratio and the Se and Hg intakes are considered, theoretically, one should attempt to avoid a situation in which the Hg-to-Se molar ratio $>1:1$ and the Hg content exceeds the standard (or the levels of Se are insufficient or excessive) because the risk factor may double in such cases. Instead, the consumption of more foods with an Hg-to-Se molar ratio $<1:1$, low Hg content and high Se content should be encouraged because foods with this combination of characteristics can produce maximum health benefits. The author has systematically investigated this topic and has proposed a new evaluation model based on the benefit-risk value (BRV), $BRV = PDI_{Se} - \Delta_{Se} - PDI_{Hg}$, in which the BRV is equal to the molar Se intake (PDI_{Se}) minus the sum of the molar Hg intake (PDI_{Hg}) and the minimum required molar Se intake (Δ_{Se}) for a human. A positive BRV that is smaller than the upper limit of safe Se intake, ∇_{Se} , indicates a beneficial state (with the antagonistic effect of Hg taken into account), and the opposite indicates a risky state (Zhang et al. 2014). The author has used this model and nine other existing evaluation methods to perform a demonstrative analysis and comparison using data collected from residents in the Wanshan Hg mine area, which has previously been studied using the conventional assessment method (Zhang et al. 2010). The results exhibited very large differences among the different assessment models, suggesting the necessity of considering the effect of Se in future assessments of the health risks of Hg exposure (see Chap. 13 for details).

It is well known that the dietary Se intake of Chinese residents is generally low because of the low levels of Se in the soil in most parts of China (Tan 1989). Fortunately, most fish consumed by Chinese residents are farmed fish with low Hg levels (Zhang et al. 2010). In combination with the very low daily fish consumption, this fact ensures that the risk of Hg exposure is generally insignificant. Therefore, residents of China need not worry unduly about the problem of MeHg exposure; instead, they should pay more attention to improving their dietary intake of Se and other nutrients. For example, increasing the daily consumption of fish can not only improve Se intake but also greatly increase the intake of other nutrients that are important for human health, especially for fetal and childhood development, such as w-3 polyunsaturated fatty acids, vitamin D and iodine. Coastal residents consume far more fish than inland residents. This segment of the population should reduce their consumption of predatory fish that are at the top of the food chain, such as sharks, octopus and tuna, because the MeHg level in predatory fish (after concentration and biomagnification) often exceeds the safe limit. In particular, whales should be avoided because they not only are at the top of the marine food chain but also have a long growth cycle; therefore, the MeHg levels in whales are expected to be much higher than those in ordinary predatory fish after biomagnification at various levels of the food chain. More importantly, compared with other marine fish, whale meat is both generally low in Se content and enriched in polychlorinated biphenyls (PCBs) and other toxic substances (Schantz et al. 1993), which increases the risk of combined exposure.

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